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ORIGINAL REPORT

Correlation of Computed Tomography and Positron Emission Tomography in Patients With Metastatic Gastrointestinal Stromal Tumor Treated at a Single Institution With Imatinib Mesylate: Proposal of New Computed Tomography Response Criteria

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Response Evaluation Criteria in Solid Tumors (RECIST) are insensitive in evaluating gastrointestinal stromal tumors (GISTs) treated with imatinib. This study evaluates whether computed tomography (CT) findings of GIST after imatinib treatment correlate with tumor responses by [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) and develops reliable, quantitative, CT response criteria.

Patients and Methods
A total of 172 lesions selected by RECIST were evaluated in 40 patients with metastatic GISTs treated with imatinib. All patients had pretreatment and 2-month follow-up CTs and FDG-PETs. Multivariate analysis was performed using tumor size and density (Hounsfield unit [HU]) on CT and maximum standardized uptake value (SUV_{max}) on FDG-PET. Patients were observed up to 28 months.

Results
Mean baseline tumor size and density on CT were 5.3 cm and 72.8 HU, respectively, and mean baseline SUV_{max} on FDG-PET was 5.8. Thirty-three patients had good response on FDG-PET. A decrease in tumor size of more than 10% or a decrease in tumor density of more than 15% on CT had a sensitivity of 97% and a specificity of 100% in identifying PET responders versus 52% and 100% by RECIST. Good responders on CT at 2 months had significantly longer time to progression than those who did not respond ($P = .01$).

Conclusion
Small changes in tumor size or density on CT are sensitive and specific methods of assessing the response of GISTs. If the prognostic value of our proposed CT response criteria can be confirmed prospectively, the criteria should be employed in future studies of patients with GIST.

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the GI tract and is distinguished from true smooth muscle or neural tumors in approximately 95% of patients by expression of the KIT receptor tyrosine kinase (CD117). GISTs are now known to originate from the precursors of the interstitial cells of Cajal in the myenteric plexus. Most GISTs occur in the stomach (50%) and the small bowel (25%), but may occur anywhere in the GI tract as well as within the peritoneum. GISTs are known to have high malignant potential and none can be labeled definitely as benign.[1]

The therapeutic options for advanced GISTs have been limited until the remarkable efficacy of imatinib (Gleevec; Novartis, Basel, Switzerland), a tyrosine kinase inhibitor, was reported.[2] Imatinib, a phenylaminopyrimidine derivative, is a small molecule that is known to inhibit the specific kinase action of ABL, the chimeric BCR-ABL fusion protein found in certain leukemias (such as chronic myelogenous leukemia), the platelet-derived growth factor receptors alpha and beta, and KIT, the product of the *c-kit* proto-oncogene.[3-5]

Table 1. Tumor Size, Density, and SUV_{max} Before and After Treatment (N = 40)

Parameter	FDG-PET SUV_{max}		CT			
			Size (cm)		Density (HU)	
	Pre	Post	Pre	Post	Pre	Post
Mean	5.8	1.4	5.3	4.2	72.8	53.8
Median	4.8	0	4.4	3.5	68.4	44.8
Range	1.4-19.7	0-13.7	2.0-16.5	1.4-13.1	45.4-156.8	10.0-135.0

Abbreviations: SUV_{max}, maximum standardized uptake value; CT, computed tomography; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; HU, Hounsfield unit; Pre, before treatment; Post, after treatment.

Since the introduction of this molecularly targeted drug, there has been increasing concern about the use of the traditional tumor response criteria.[6-9] Our recent study indicated that the current international tumor response criteria, Response Evaluation Criteria in Solid Tumors (RECIST),[10] using anatomic information only (tumor size), significantly underestimated the initial tumor response to imatinib in patients with metastatic GISTs.[11] At the same time, dramatic changes were noted in tumor density, enhancing intratumoral tumor nodules, and tumor vessels on contrast-enhanced computed tomography (CT) images after imatinib treatment. Among these parameters, tumor density, as determined by measuring CT attenuation coefficient (Hounsfield unit [HU]), together with minor changes in tumor size that were insufficient for response by RECIST, provided the consistent quantitative means to evaluate the tumor response.[8,9]

Positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG) has been suggested as an early, sensitive marker of tumor response to anticancer drugs by monitoring the changes in glucose metabolism in tumors.[12,13] Recently, FDG-PET has shown to be highly sensitive in detecting early response[6,7,14] and to be useful to predict the long-term response of GIST to imatinib mesylate in patients with metastatic CD117-positive GIST.[7,10,14] Unfortunately, access to PET is still limited for patients with GISTs, and in some lesions, the glucose uptake before treatment is not sufficient to be detected by FDG-PET. Our recent study showed that 36 (21%) of 173 lesions, ranging from 1.0 to 4.7 cm, did not demonstrate appreciable glucose uptake on pretreatment FDG-PET.[11] Furthermore, the currently available European Organization for Research and Treatment of Cancer 1999 tumor response criteria[12] that defined partial response by PET as a 25% decrease in maximum standardized uptake (SUV_{max}) may not be suitable for evaluating patients with GIST treated with imatinib mesylate. A recent study has demonstrated that, in good responders to imatinib, the absolute value of SUV_{max} decreased to below 2.5.[14] This is similar to our recent observations. We have also observed a mean decrease of greater than 90% with a minimum of 65% in SUV_{max} in good responders (unpublished data).

The purposes of the study were to determine whether the changes on CT in advanced GIST after treatment with imatinib correlated with the changes in glucose metabolism on FDG-PET when a more than 70% decrease in SUV_{max} to an absolute value of less than 2.5 was used to define a good response, and to determine if CT criteria could be used in quantitative response evaluation and possibly as prognostic indicators.

PATIENTS AND METHODS

Patients

A total of 109 patients with metastatic GIST treated with a daily dose of 400 to 800 mg of imatinib at The University of Texas M.D. Anderson Cancer Center during the period of December 2000 to September 2001 were selected for this analysis. Among these, 106 patients were enrolled onto the Intergroup phase III study and three were treated on the basis of compassionate use of an investigational new drug (use of an investigational new drug outside of an ongoing clinical trial under US Food and Drug Administration and institutional approval). The studies were conducted under the approval of the institutional review board, and all of the patients who participated signed informed consent forms. Forty-four patients of 109 had both CT and FDG-PET at our institution within 1 week of each other before treatment and at 2 months after treatment. Among these, four patients were excluded due to lack of measurable lesions by RECIST definitions. A total of 172 lesions in 40 patients were selected on the basis of RECIST[10] for this study: 107 in the liver, 59 in the peritoneal cavity, two in the abdominal wall, and four in the pleura. Lesions smaller than 1.5 cm were excluded. There were 19 males and 21 females, with an age range of 28 to 86 years. All 40 patients were observed with CT up to 28 months after treatment.

Table 2. Relationship Between the Change in Tumor Size and Density on CT and Tumor Response by FDG-PET

Tumor Response by FDG-PET (N = 40)	Tumor Size			Tumor Density				
		≥ 10% Decrease			≥ 15% Decrease		≥ 10% Decrease in Tumor Size or a > 15% Decrease in Tumor Density	
	Mean % Change	No. of Patients	%	Mean % Change	No. of Patients	%	No. of Patients	%
Good (n = 33)	−26	31	94	−31	27	82	32	97
Poor (n = 7)	10	0	0	−6	0	0	0	0

Abbreviations: CT, computed tomography; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography.

Table 3. Modified CT Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions
	No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT
	No new lesions
	No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD
	No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT
	New lesions
	New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.[10]

Imaging Techniques

CT was performed with a Light Speed or Hi-Speed Advantage helical scanner (GE Medical Systems, Milwaukee, WI) using a monophasic scanning technique. We scanned the abdomen and pelvis at 7.0- or 7.5-mm scanning collimation, starting from the level of the diaphragm to the pubic symphysis. The scan delay was 60 seconds after the start of administration of 150 mL of 60% nonionic contrast agent (Optiray 320; Mallinckrodt Inc, St Louis, MO) at a rate of 3 mL/sec. In 11 patients, a triphasic scanning technique was used, with scan delays of 20, 40, and 60 seconds for the early arterial, late arterial, and portal venous phases, respectively, after intravenous injection of the contrast agent at a rate of 5 mL/sec.

FDG-PET was performed using a CTI HR+ PET scanner (Siemens Inc, Knoxville, TN) after administration of 10 to 15 mCi of [^{18}F]FDG. All patients had nothing by mouth at least 6 hours before being scanned. After a 60-minute uptake phase, patients were scanned from the neck to the pelvis, according to the following parameters: 5-minute emission scan and 3-minute transmission scan (for attenuation correction) per field of view in a two-dimensional mode. The images were interpreted using volumetric projection and multiple orthogonal projection analysis.

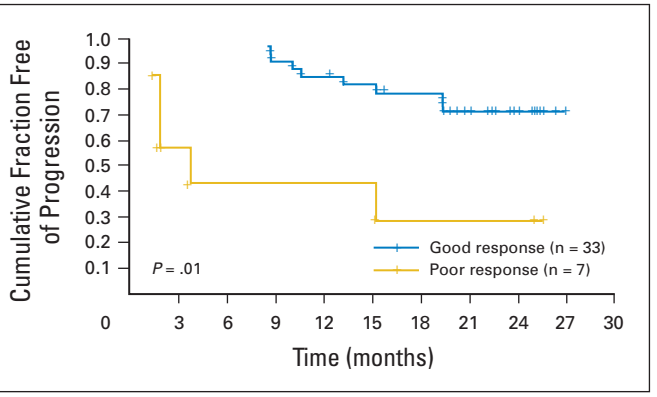

Fig 2. Time to tumor progression in good and poor responders by positron emission tomography (PET) response criteria. When the tumor response was evaluated on the basis of PET response criteria, a significant difference was observed in the long-term prognosis between the good and poor responders (P = .01) for up to 28 months.

Data Analysis

Multivariate analysis was performed using the following parameters from CT and FDG-PET: the size (in centimeters) and attenuation coefficient (HU) of the tumor on CT images; SUV_{max} values on FDG-PET images of each lesion corresponding to those on CT images; and time to tumor progression (TTP) recorded for all patients up to 28 months after treatment.

Tumor size. Tumor size was measured in the longest cross-sectional dimension for each lesion at each time point using an Advanced workstation (GE Medical Systems). Based on RECIST, the sum of the longest dimensions of selected lesions in each patient was computed, and the absolute and percent changes of the sum from the pretreatment evaluation to the 2-month evaluation were computed for each patient. The changes in tumor size of each patient were then correlated with the changes in SUV_{max} on FDG-PET.

CT attenuation coefficients. On an Advanced Workstation (GE Medical Systems), we measured the CT attenuation coefficient (density) of each tumor in HU by drawing a region of interest around the margin of the entire tumor. In the cases in which the patients were scanned with triphasic techniques, the portal venous phase was used for the tumor density measurement.

The tumor density measurements of all lesions were combined and a mean HU for each patient was computed. Then, the absolute and percent changes in CT density from the pretreatment evaluation to the 2-month evaluation were computed for each patient. The changes in HU of each patient were then correlated with the changes in SUV_{max} on FDG-PET. The reliability

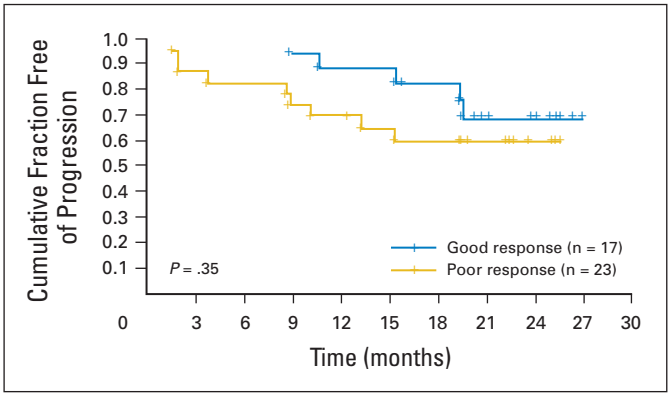

Fig 1. Time to tumor progression in good and poor responders by Response Evaluation Criteria in Solid Tumors (RECIST). When the tumor response was evaluated on the basis of RECIST at the time of the best response after treatment, no significant difference was observed in long-term prognosis between the good and poor responders (P = .35) for up to 28 months.

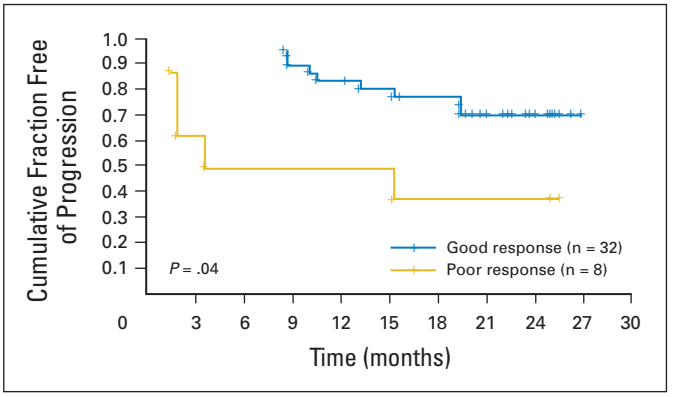

Fig 3. Time to tumor progression in good and poor responders by new computed tomography (CT) response criteria. When the tumor response was evaluated on the basis of a combination of tumor sizes and tumor density on CT, a significant difference was observed in the long-term prognosis between the good and poor responders (P = .04) for up to 28 months.

Table 4. Response Rates by RECIST, FDG-PET, and Modified CT Criteria (N = 40)

Outcome	RECIST	FDG-PET	CT
Responders (n)	17	33	32
Nonresponders (n)	23	7	8
Response rate (%)	43	83	80

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; CT, computed tomography.

of different monitors (CT operator's consoles, Advanced Workstation, and Stentor workstations [Stentor Inc, Brisbane, CA] in a radiologist's office) was tested before measuring the CT attenuation coefficient of tumors on CT. On the basis of our initial analysis,[11] the absolute values of HU of each lesion were chosen for tumor density measurement.

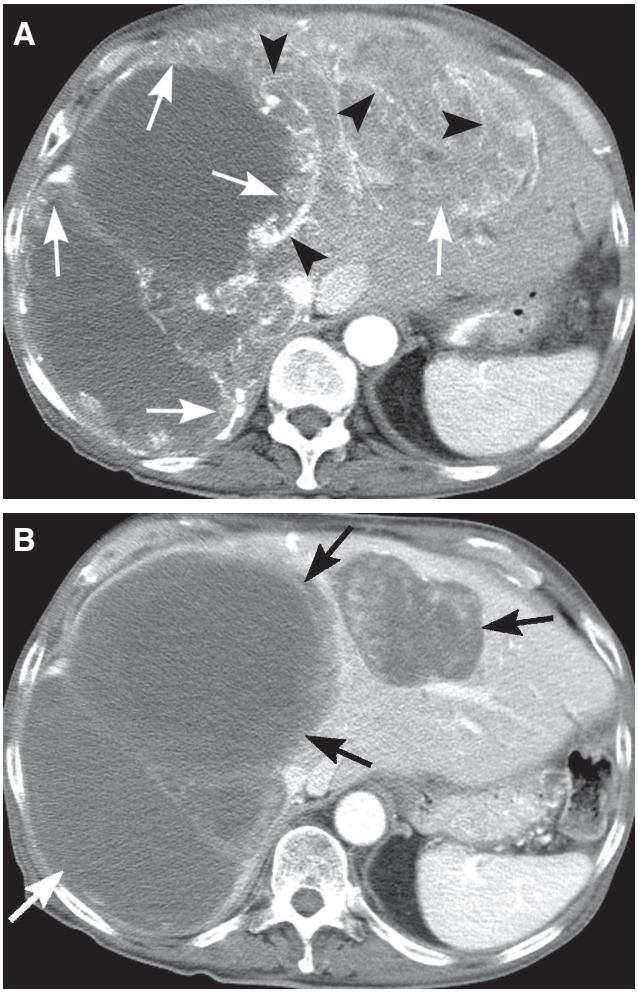

Fig 4. A 77-year-old man with primary gastrointestinal stromal tumors of the stomach and multiple hepatic metastases. (A) Pretreatment computed tomography (CT) scan shows large hepatic masses on a late arterial-phase image with hyperdense tumor nodules (→) along the periphery. Note the multiple prominent tumor vessels (arrowheads). (B) CT scan obtained 2 months after treatment shows that the lesions (→) have become significantly hypodense. The enhancing tumor nodules have almost completely disappeared and tumor vessels are no longer detectable.

SUV on FDG-PET. Using vendor-specific software for Siemens/CTI HR+ PET scanner, SUV_{max} was measured by drawing a region of interest slightly outside each lesion corresponding to those used for HU measurement on the CT image and adjusted for body weight. The SUV_{max} values of all tumors were combined, and a mean SUV_{max} was computed for each patient. Then, the absolute and percent changes from the pretreatment evaluation to the 2-month evaluation were computed for each patient. The values of SUV_{max} that were decreased by at least 70%, to less than 2.5 at 2 months after treatment, were graded as good responses (GoodR). All other responses, including stable or any increase in SUV_{max}, were considered poor responses (PoorR).

TTP. Tumor progression was identified on the basis of the following CT findings: appearance of new lesions or metastasis, appearance of new intratumoral tumor nodules or increase in the size of existing intratumoral tumor nodules, or increase in overall tumor size by more than 20% in the absence of post-treatment hypodense change.

Statistical Analysis

Mean percent changes in tumor size and tumor density were calculated for GoodR and PoorR groups. Then, the values of mean percent changes in tumor size and tumor density that could separate these two groups best were identified. The changes in tumor size and tumor density on the basis of these new CT criteria were then correlated with the tumor response evaluated by the PET criteria. To evaluate the ability of RECIST, PET criteria (SUV_{max}), and new CT criteria (tumor density and size) in predicting the long-term prognosis, TTPs were compared between the groups, with GoodR and PoorR categorized by each response criterion, by using a log-rank test.

RESULTS

In 40 patients, the average SUV_{max} on FDG-PET in each patient ranged from 1.4 to 19.7 (mean, 5.8) before treatment and from 0 to 13.7 (mean, 1.4) at 2 months after treatment. Tumor size ranged from 2.0 to 16.5 cm (mean, 5.3 cm) before treatment and from 1.4 to 13.1 cm (mean, 4.2 cm) at 2 months post-treatment on CT. Tumor density ranged from 45.4 to 156.8 HU (mean, 72.8 HU) before treatment and from 10.0 to 135.0 HU (mean, 53.8 HU) at 2 months after treatment (Table 1).

Thirty-three (83%) of 40 patients showed GoodR on FDG-PET (Table 2). In good responders, tumor size decreased by a mean of 26% at 2 months after treatment, and 31 patients (94%) demonstrated a more than 10% decrease in tumor size. No patient with PoorR showed a more than 10% decrease in tumor size (Table 2). In good responders, tumor density (HU) decreased by a mean of 31% at 8 weeks after treatment, and 27 patients (82%) demonstrated a more than 15% decrease in HU. No patient with PoorR showed a more than 15% decrease in HU (Table 2). Ninety-seven percent of good responders showed either a 10% decrease in tumor size or a 15% decrease in tumor density on CT, but none in the PoorR group showed either 10% decrease in tumor size or 15% decrease in tumor density (Table 2). On the basis of these results, the new CT criteria for good response on CT were defined as follows: a more than 10% mean percent decrease in tumor size or a more than 15% mean percent decrease in tumor density (Table 3).

When RECIST were used in tumor response evaluation (best response, regardless of the time when it was defined), no significant difference was observed in long-term prognosis (TTP) between the good and poor responders ($P = .35$) for up to 28 months in both groups (Fig 1). When PET criteria or CT criteria of either a more than 10% decrease in maximum diameter or a more than 15% decrease in tumor density at 2 months after treatment were used, significant

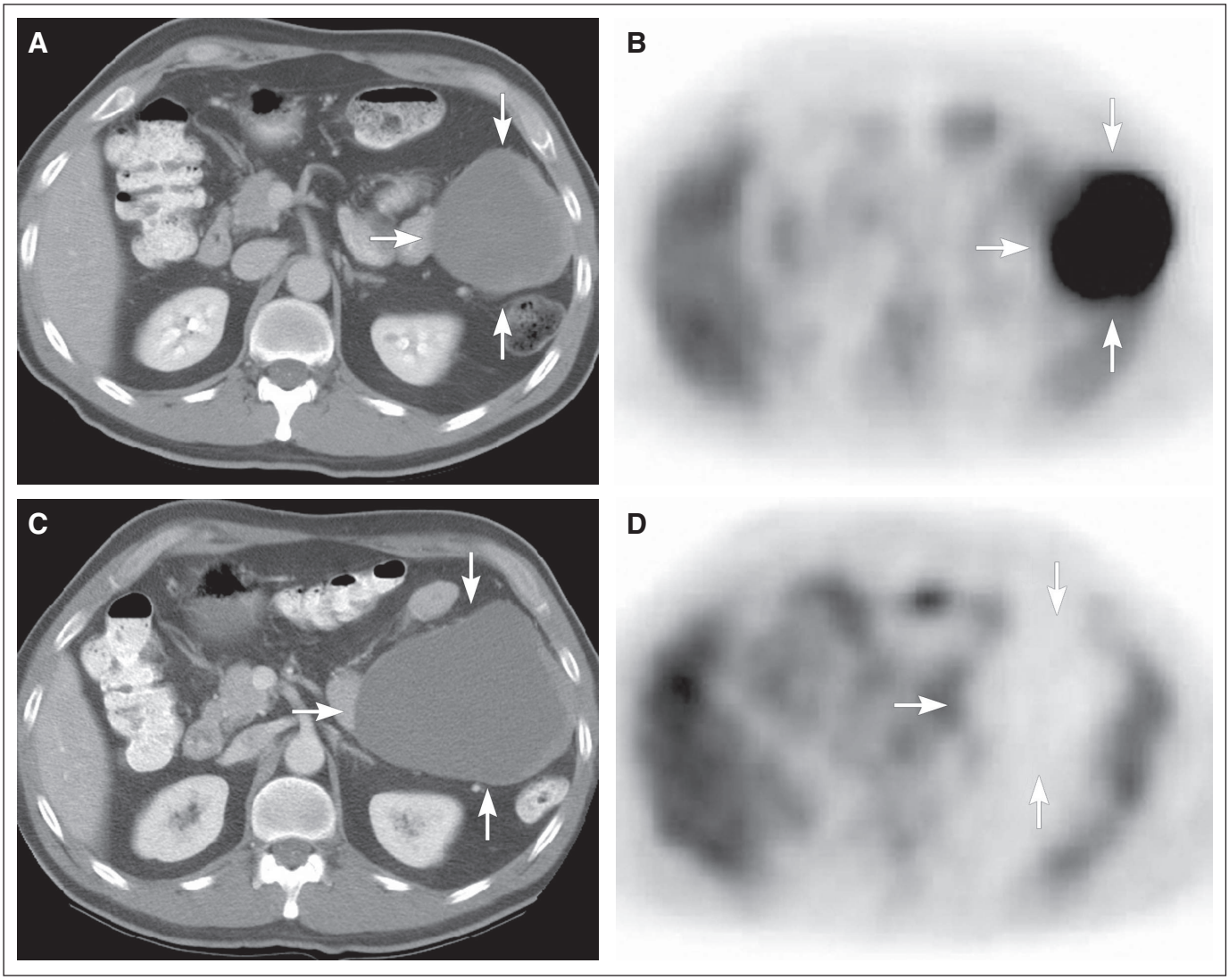

Fig 5. A 51-year-old male with primary gastrointestinal stromal tumors of colon and recurrent peritoneal metastases. Pretreatment computed tomography (CT) scan shows (A) a relatively low-density peritoneal mass (42 Hounsfield units [HU]) (→) corresponding to (B) a lesion with markedly increased glucose uptake (→) on positron emission tomography using [^{18}F]fluorodeoxyglucose (FDG-PET). At 2 months after treatment, (C) the mass (→) has become larger, however, the CT density has decreased (30 HU), (D) with no appreciable glucose uptake (→) on FDG-PET, corresponding to clinical improvement. (Reprinted with permission.[11])

differences were observed in TTP between good and poor responders ($P = .01$ and $P = .04$, respectively) for up to 28 months (Figs 2 and 3). When the new CT criteria were used, 32 of 40 (80%) patients responded to imatinib, whereas when RECIST were used, 17 of 40 patients (43%) responded to imatinib (Table 4).

DISCUSSION

The treatment response of solid tumors traditionally has been evaluated on the basis of morphologic features (tumor size). RECIST partial response, a more than 30% decrease in the sum of the maximum diameters of all measurable lesions, is the current standard in assessing the response of solid tumors to anticancer therapy.[10] These criteria were modified from older criteria that used a more than 50% decrease in the sum of the products of perpendicular diameters of all measurable lesions.[15,16] Historical perspective of use of a more than 50% decrease in the products of perpendicular diameters as a partial response criterion goes back to the 1970s. A more than 50% decrease was accepted as a partial response criterion on the basis of an experiment of tumor measurement conducted by 16 clinicians, using solid spheres covered by foam rubber pads.[17] Now that we can measure the size of lesions to a precision of tenths of millimeters with a computer on the cross-sectional images, such as CT or magnetic resonance imaging, the accuracy of current response criteria should be re-examined.

The current response evaluation criteria by FDG-PET adopted by the European Organization for Research and Treatment of Cancer were developed on the basis of multiple previous small studies of various tumors.[12] GIST was not included. The definition of partial response as a 25% decrease in SUV_{max} is based on the reproducibility of the SUV_{max} measurement,[12] similar to the 50% size decrease on physical examination,[17] rather than any correlation with clinically relevant end points such as TTP. Recently, Van den Abbeele et al[14]

reported that patients with an early decrease in an absolute value of SUV_{max} to less than 2.5 at 21 to 40 days after treatment with imatinib demonstrated a significantly better long-term progression-free survival relative to others. Jager et al[18] reported that a decrease in SUV_{max} by 65% at 1 week after treatment indicated good responders. In our review, all responders demonstrated greater than 75% decrease in SUV_{max} at 2 months after treatment with imatinib mesylate, except for one who showed a 64% decrease. For this study, we used PET criteria of a more than 70% decrease in SUV_{max} relative to the pretreatment value, to an absolute value of SUV_{max} to less than 2.5, to be a good responder.

This study confirmed our previous observation[9] that RECIST significantly underestimated tumor response. Our data suggest that a more than 10% decrease in one dimension on CT at 2 months after treatment is adequate to identify good responders on FDG-PET and predicts a longer TTP. Furthermore, contrast-enhanced CT can demonstrate tumor characteristics, such as tumor density, enhancing tumor nodules, and tumor vessels, in addition to tumor size (Fig 4; Appendix Fig A1, online only). It is clear that the outside dimensions of a tumor mass may not accurately reflect how active the tumor is. Some lesions, despite clinical and PET response, actually increased in size (Fig 5). Decreased density of the responding tumors on CT is correlated with the development of tumor necrosis or cystic or myxoid degeneration. Tumor density also provides an additional measure of response to therapy, can be quantified objectively, and can be measured readily on clinical images (Figs A1 and 5). Once the CT technique is designed to provide an optimal portal venous phase (the time for the maximum hepatic enhancement and the best visualization of most lesions) for a specific scanner, and if the same CT technique is used for pre- and post-treatment evaluations, density measurement should be reproducible on an accurately calibrated workstation. Of note, however, is that arterial phase (bi- or triphasic dynamic imaging technique), although not used for density measurement, is also needed to optimize the visualization of all lesions and to observe changes in tumor vascularity and the pattern of enhancement before and after treatment.[11]

A combination of the values of tumor size and tumor density on CT (a 10% decrease in tumor size or a more than 15% decrease in tumor density at 2 months of treatment) predicted the TTP as well as the SUV_{max}. In our patients with metastatic GISTs, response evaluated by the new CT criteria was a significantly better predictor of TTP than ultimate partial response by RECIST (Table 4; Fig 3). We have also observed the inadequacy of RECIST in identifying responding tumors in other solid tumors, such as renal cell carcinomas (C.C., H.C.) or other sarcomas (R.S.B.), sporadically. This inadequacy seems particularly evident in patients undergoing targeted therapies, such as antiangiogenic agents or tyrosine kinase inhibitor treatments.[19-21] In an early thalidomide trial at our institution, responding tumors showed significant changes in tumor perfusion without enough change in size to be classified as partial reasponse by RECIST (unpublished data). Similarly, changes in CT density of responding tumors have been published previously. In an SU11248 trial by Motzer et al,[21] the responding metastatic renal cell tumors in the liver showed dramatic decrease in enhancement with little change in size on post-treatment CT. Although our criteria were derived from treatment of GIST with imatinib, these criteria might apply to other tumor types and to cytotoxic as well as targeted therapy.

In conclusion, CT was a sensitive and specific method to assess the response of metastatic GISTs to imatinib: a decrease in tumor size of more than 10% or a decrease in tumor density of more than 15% had a sensitivity of 97% and a specificity of 100% in detecting patients with GoodR evaluated by PET criteria. These CT criteria were excellent predictors of tumor progression, as were PET criteria. RECIST substantially underestimated, especially at the early stage of treatment, the effect of imatinib on metastatic GIST and was a poor predictor of clinical benefit. These data can serve as a training set for the prognostic value of response with regard to TTP to be confirmed in an independent group of patients. If confirmed for GIST, extrapolation of these data to other tumors and other treatment approaches requires additional study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).